

CLAIMS

What is claimed is:

1. A method of promoting recruitment, proliferation, differentiation, migration or survival of neuronal cells or neuronal precursor cells in a mammalian subject comprising administering to the subject a composition comprising a vascular endothelial growth factor C (VEGF-C) product or a vascular endothelial growth factor D (VEGF-D) product.
2. The method of claim 1 further comprising a step, prior to the administering step, of identifying a mammalian subject in need of neuronal cell or neuronal precursor cell recruitment, proliferation, or differentiation.
3. The method of claim 2 wherein the VEGF-C product comprises a purified mammalian prepro-VEGF-C polypeptide, VEGF-C Δ N Δ C, VEGF-C Δ C₁₅₆, VEGF-C Δ N Δ C C156S, a chimeric heparin-binding VEGF-C, or a fragment of the prepro-VEGF-C polypeptide that binds a VEGF-C receptor, wherein the VEGF-C receptor is selected from the group consisting of VEGFR-3, VEGFR-2, neuropilin-1 and neuropilin-2.
4. The method of claim 3 wherein the subject and the prepro-VEGF-C polypeptide are human.
5. The method of claim 4 wherein the VEGF-C product comprises a fragment of human prepro-VEGF-C that contains amino acids 32-227 of SEQ ID NO: 24.

6. The method of claim 2 wherein the VEGF-C product comprises a polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising a nucleotide sequence that encodes the human VEGF-C amino acid sequence of SEQ ID NO: 24;

(b) a polynucleotide comprising a nucleotide sequence at least 90% identical to the nucleotide sequence of SEQ ID NO: 23 and encodes a polypeptide that binds VEGFR-3;

(c) a polynucleotide comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence at least 90% identical to SEQ ID NO: 24, wherein the polypeptide binds VEGFR-3;

(d) a polynucleotide that hybridizes to the complement of SEQ ID NO: 23 under the following stringent conditions and encodes a polypeptide that binds VEGFR-3: 2 x SSC/0.1% SDS twice at RT, 1 x SSC/0.1% SDS 15 min at 55° C, 0.1 x SSC/0.1%SDS 15 min at 55° C.

(e) fragments of (a) - (d) that encoded a polypeptide that binds VEGFR-3.

7. The method of claim 2, wherein the VEGF-C product comprises a polynucleotide that encodes a VEGF-C polypeptide set forth in SEQ ID NO: 24 or fragment thereof that binds VEGFR-3.

8. The method of claim 6 or 7, wherein the VEGF-C product comprises a viral vector containing the polynucleotide.

9. The method of claim 8, wherein the vector comprises a replication-deficient adenovirus, adeno-associated virus, or lentivirus.

10. A method according to claim 2 wherein the composition further comprises a pharmaceutically acceptable carrier.

11. A method of stimulating neural stem cell proliferation or differentiation, comprising,
 - obtaining a biological sample from a mammalian subject, wherein said sample comprises neural stem cells, and
 - contacting the neural stem cells with a composition comprising a vascular endothelial growth factor C (VEGF-C) product or a vascular endothelial growth factor D (VEGF-D) product
12. A method according to claim 11, wherein the contacting comprises culturing the stem cells in a culture containing VEGF-C product or VEGF-D product.
13. A method according to claim 11, further comprising a step of purifying and isolating the neural stem cells from the sample before the contacting step.
14. A method according to any one of claims 11-13, further comprising a step of purifying and isolating neural stem cells or neural cells after the contacting step.
15. Purified and isolated neural cells cultured according to claim 14.
16. The method according to claim 13, further comprising a step of administering the neural stem cells to the mammalian subject after the contacting step.
17. The method according to claim 13, further comprising a step of transplanting the neural stem cells into a different mammalian subject after the contacting step.

18. The method of claim 16 or 17, wherein the cells are seeded into a tissue, organ, or artificial matrix *ex vivo*, and said tissue, organ, or artificial matrix is attached, implanted, or transplanted into the mammalian subject

19. A method of inducing neural stem cell proliferation *in vitro* comprising contacting the neural stem cell with a composition comprising a VEGF-C product or a VEGF-D product, wherein the neural stem cell is selected from the group consisting of C17.2, purified neural stem cells, HSN-1 cells, fetal pig cells, neural crest cells, bone marrow derived neural stem cells, hNT cells and a human neuronal progenitor cell line.

20. A method according to claim 19, further comprising a step of administering the stem cells to a mammalian subject after the contacting step.

21. The method of claim 19, wherein the cells are seeded into a tissue, organ, or artificial matrix *ex vivo*, and said tissue, organ, or artificial matrix is attached, implanted, or transplanted into a mammalian subject.

22. The method of claim 16, 17, or 20 wherein the mammalian subject is human.

23. The method of claim 1 or 16 wherein the VEGF-C or VEGF-D product is administered in conjunction with a neural growth factor.

24. The method of claim 23 wherein the neural growth factor is selected from the group consisting of interferon gamma, nerve growth factor, epidermal growth factor (EGF), basic fibroblast growth factor (bFGF), neurogenin, brain derived neurotrophic factor (BDNF), thyroid hormone, bone morphogenic proteins (BMPs), leukemia inhibitory factor (LIF), sonic hedgehog, glial cell line-derived neurotrophic factor (GDNFs), vascular endothelial growth factor (VEGF), interleukins, interferons,

stem cell factor (SCF), activins, inhibins, chemokines, retinoic acid and ciliary neurotrophic factor (CNTF).

25. A method according to claim 1 or 16, wherein the subject has a disease or condition characterized by aberrant growth of neuronal cells, neuronal scarring, or neural degeneration.

26. A method according to claim 25, wherein the neural degeneration is caused by a neurodegenerative disorder selected from the group consisting of is Alzheimer's disease, Parkinson's disease, Huntington's disease, motor neuron disease, Amyotrophic Lateral Sclerosis (ALS), dementia and cerebral palsy.

27. A method according to claim 1 or 16, wherein the disease or condition is selected from the group consisting of neural trauma or neural injury.

28. The method of claim 27, wherein the neural trauma is selected from the group consisting of stroke-related injury, spinal cord injury, post-operative injury and brain ischemia.

29. The method of claim 1 or 13 wherein the VEGF-C product is administered in conjunction with a neurotherapeutic agent.

30. The method of claim 29 wherein the neurotherapeutic agent is selected from the group consisting of tacrine (Cognex), donepezil (Aricept), rivastigmine (Exelon), galantamine (Reminyl), cholinesterase inhibitors and anti-inflammatory drugs.

31. The method of claim 29 wherein the neurotherapeutic agent is selected from the group consisting of anti-cholinergics, dopamine agonists, catechol-O-methyltransferases (COMTs), amantadine (Symmetrel), Sinemet®, Selegiline, carbidopa, ropinirole (Requip), coenzyme Q10, Pramipexole (Mirapex) and levodopa (L-dopa).

32. A method of inhibiting growth and progression and of neuroblastoma and neural tumors comprising administering to a subject having a neuroblastoma or neuronal tumor a composition comprising a VEGF-C inhibitor.

33. The method of claim 32 wherein the VEGF-C inhibitor is selected from the group consisting of a polypeptide comprising an extracellular fragment of VEGFR-2 that binds to VEGF-C, VEGF-C neutralizing antibodies, VEGF-C antisense molecules, siRNA, and small molecule inhibitors.

34. The method of claim 32 wherein the VEGF-C inhibitor is selected from the group consisting of a polypeptide comprising an extracellular fragment of VEGFR-3 that binds to VEGF-C, an extracellular fragment of NRP-1 that binds to VEGF-C, and an extracellular fragment of NRP-2 that binds to VEGF-C.

35. A composition comprising a VEGF-C product and a neural growth factor in a pharmaceutically acceptable diluent or carrier.

36. A composition comprising a VEGF-C product and a neurotherapeutic agent in a pharmaceutically acceptable diluent or carrier.